IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Olle KORSGREN et al

Application No. **09/890,936**

Filed: **November 7, 2001**

NOVEL USE WITH TRANSPLANTATION SURGERY

Examiner: **Donna A. Jagoe**

Art Unit: **1614**

APPEAL BRIEF

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

The present appeal is taken from the final rejection mailed May 22, 2008, of claims 4, 8, 9, 11, and 27. A clean copy of these claims, double spaced, appears in the appendix to this brief.

REAL PARTY IN INTEREST

The assignee of the present application Corline Systems AB of Uppsala, SWEDEN.

RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

STATUS OF CLAIMS

Claims 4, 8, 9, 11 and 27 are rejected, and all of these claims are appealed.

Claims 14 and 26 are withdrawn from consideration.

Claims 1-3, 7, 10, 12, 13 and 15-25 are canceled.

STATUS OF AMENDMENTS

All amendments have been entered.

SUMMARY OF CLAIMED SUBJECT MATTER

The present invention, as recited in the two independent claims 4 and 27, relates to the transplantation of insulin producing cells into a patient suffering from insulin dependent diabetes mellitus (IDDM), wherein the cells (islets) so transplanted have been modified by irreversible adsorption with heparin or a fraction or derivative thereof onto the surfaces of the individually isolated islets. This coating takes place from an aqueous solution of the heparin, e.g. Corline Heparin Conjugate, with the result of obviating the significant problem of clotting.

It will be pointed out in the "argument" section below that it was the applicants who discovered that clotting was a major problem as to why islet transplantation has been unsuccessful in the past.

I. -Concise Explanation of the subject matter of Independent claim 4.

Claim 4, in its first paragraph, calls for a method comprising transplantation of insulin producing cells in the form of individually isolated islets to a patient suffering from insulin dependent diabetes mellitus (IDDM):

The first paragraph of the appellants' specification states that the invention "is with the field of transplantation surgery" and "relates to use of a clotting preventing agent in the production of a drug for administration in association for transplantation of cells…, such as insulin producing cells to patients with insulin dependent diabetes mellitus, IDDM." Also see the top paragraph at page 4 of the Appellants' specification.

That the islets or cells are "isolated" is explicit in the second paragraph on page 3, and the fourth line of example 1 on page 6; and that "isolated" means "individually isolated" is confirmed in the declaration of independent expert Professor James Shapiro, MD, PhD, executed December 8, 2007, and filed in the present application with the reply of December 10, 2007. It is also confirmed in the third declaration of co-invention Rolf Larsson, PhD, executed November 29, 2007, and also filed with the reply of December 10, 2007, noting especially paragraph (5).

In its second paragraph, claim 4 recites that the "individually isolated islets are modified by irreversible absorption with a clotting inhibiting agent comprising heparin or a fraction or derivative thereof onto the surfaces of the islets"; and the third paragraph on page 3 of Appellants' specification mentions that "the clotting preventing agent is an anticoagulant, such as heparin or fractions or derivatives thereof." In the immediately following paragraph (fourth

paragraph on page 3) it is stated that the "islet cells are coated with heparin or fractions or derivatives thereof by preincubation of islets in a solution containing heparin or fractions or derivatives thereof" and further mentions the use of "a conjugate of heparin to coat the islets." That the isolated islets are modified by irreversible absorption is supported by the first sentence of example 3 at the bottom of page 9 of Appellants' specification.

In its third paragraph, claim 4 further recites that the "individual cells are each separately coated with heparin or a fraction or derivative thereof by pre-incubation of islets in an aqueous solution containing heparin or a fraction or derivative thereof":

Again, the fourth paragraph on page 3 of Appellants' specification indicates that the islets are coated with heparin or a conjugate thereof, and also mentions that this is "by preincubation of islets in a solution...." Reference to "soluable heparin" as in the title of example 1 (page 6) means an aqueous solution as indicated in the sentence spanning pages 9 and 10 (example 3) and the fact that Corline Heparin Conjugate, as disclosed in WO 93/05793, incorporated by reference into the present specification in the second paragraph on page 6, comprises an aqueous solution.

Claim 4 concludes with reciting that the "clotting inhibiting agent acts to inhibit clotting or reduce clotting":

The fourth paragraph on page 3 mentions the effect of the reduction of clotting, and the top paragraph on page 4 mentions the prevention of clotting. Also, again please see the second paragraph on page 6, as well as the experimental results shown in the working examples.

II. -Concise Explanation of the subject matter of Independent claim 27.

The preamble for claim 27 is the same as that of claim 4, and so the concise explanation of the preamble is respectfully repeated by reference to that submitted above.

The second paragraph of claim 27 is the same as the second paragraph of claim 4, except for a typographical error, i.e. in the third line of the second paragraph of claim 27, the word "thereon" should be "thereof". As the concise explanation for the second paragraph of claim 27 is the same as that for claim 4, the concise explanation of such second paragraph of claim 4 is respectfully repeated by reference.

The third paragraph of claim 27 recites "said modification comprising incubating said islets in a solution of heparin or a fraction of derivative thereof." Another typographical error appears here in that the word following "fraction" should be "or", rather than "of". Appellants' would hope to be able to correct the typographical errors in this claim.

At any rate, incubating the islets in a solution of heparin is clearly supported in the fourth paragraph on page 3 of Appellants' specification.

Like claim 4, claim 27 concludes with the recitation that the "clotting inhibiting agent acts to inhibit clotting or reduce clotting", supported for example by the fourth paragraph on page 3 and the top paragraph on page 4 of Appellants' specification.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Main claims 4 and 27, and dependent claims 8 and 11 are rejected under Section 102 as anticipated by Wagner et al, DE 196 23 440 (Wagner).

Main claims 4 and 27, and dependent claims 8 and 11, are also rejected under Section 102 as anticipated by Soon-Shiong et al, USP 5,705,270 (Soon-Shiong).

Main claim 4 and dependent claims 8 and 11 are rejected under Section 102 as anticipated by Nomura et al, "Unpurified islet cell transplantation in diabetic rats," Transplantation Proceedings, Vol. 28, No. 3 (June , 1996), pp. 1849-1850 (Nomura).

Claim 9 is rejected under Section 103 as obvious from Soon-Shiong "and" Wagner "as applied to claims 4, 8, 11, and 27…, and further in view of Couser et al", "The Effects of Soluable Recombinant Compliment Receptor I on Compliment-Mediated Experimental Glomerulonephritis", Journal of the American Society of Nephrology (1995), Vol. 5, No. 11, pp. 1888-1894 (Couser).

ARGUMENTS

Appellants' respectfully maintain that the references applied under Section 102 do not anticipate any of appellants' claims, and that the proposed combination or combinations applied under Section 103, even if such combination or combinations were obvious, would not result in the claimed subject matter.

I. -Background

As pointed out in the second paragraph on page 1 of Appellants' specification, transplantation of isolated islets has proven to be considerably less successful compared to whole pancreas transplantation, and yet "there is no obvious immunological explanation as to why transplantation of whole pancreas is more successful than islet transplantation."

As pointed out in the bottom paragraph on page 2 of Appellants' specification, the present invention is based on experiments performed by the Appellants "implying adding human, adult porcine or fetal porcine islets to human whole blood" and being "struck by the vigorous coagulation occurring when these islets were injected into human ABO-compatible blood." Based on their microscopical examinations, it became evident to them "that the islets are rapidly coated by a layer of platelets which soon develops into an organized thrombus." This biological event has previously not been considered and

is now suggested to be a major explanation as to why the outcome of autologous islet transplantation has been comparatively unsuccessful." The present invention is based on this new discovery.

II. -What the prior art discloses

The Wagner disclosure is not very clear. Nevertheless, the following text appears on page 4 of the Wagner translation near the bottom of the page:

> Normoglycemia with the objective of a timely and need-based release of insulin is possible only by a biological replacement of the insulin producing islet cell apparatus through the pancreas or by **islet cell transplantation.** Free allogenic transplants require intensive immunosuppression. This is why it could possible to develop "bio-artificial pancreas" successfully in a growing number of patients by a biological replacement of an organ i.e. by **using isolated islet cells of a pig.** In addition to this, above mentioned immunosuppression can be prevented by using immuno-separation membranes. [Emphasis believed to be that of the Examiner]

From this, it appears that Wagner wishes to develop a "bio-artificial pancreas" by encapsulating isolated islet cells of a pig using immuno-separation membranes, and this is further mentioned on page 5 of the translation under the headings "Objective" and "Bio-artificial pancreas":

> Insulin producing cells that react to glucose stimulants by a timely or need-based release of insulin are implanted in a diabetic organism. The artificial membranes protect the free islet cells of allogenic or kenogenic origin from being destroyed by the

> immune system of the receiver. Two different forms of membranes based on diffusive soft transport that are being discussed presently.
>
> 1. Macro-capsulation is capillary membranes (Diagram 1): Here, the islets are capsulated into capillary membranes with diameters ranging from **0.5 to 4 mm and length between 2 and 3 cm** and these are then implanted in the free abdominal cavity. [Emphasis added]
>
> ...
>
> 2. Micro - capsulation: In micro - capsulation, individual islets are enclosed in the smallest possible capsules made of alginate complexed with polylysine and transplanted. The microcapsules have a diameter of **0.5mm**. This technique is very popular because experiments on animals have shown that this technique increases the survival time of the transplant substantially in comparison to the non-capsulated islets in the control tests. The results however cannot be reproduced in a uniform manner...[Emphasis added]
>
> 3. Most of the microcapsules of a diameter of half a millimeter have a volume several times larger than that of the islets of Langerhans, **which are 50 - 300 µm in size.** Narrower the membranes are to an islet, or the smaller a microcapsule is, the better they are for nourishment and insulin - release at the expected conditions. This also means that thin and closely fitting membranes can be implanted in other compartments with better oxygenation. [Emphasis added]

It is clear that Wagner is disclosing encapsulation of the islets, that the microcapsules have a diameter of 0.5 mm, and "have a volume several times larger than that of the islets…, which are 50-300 µm in size."

At the bottom of page 11 of the translation, there is mention of "pharmacotherapy with anticoagulants, platelet

aggregation inhibitors, and plasminogen activators." No mention is made of heparin until claim 7 which says that, in accordance with claim 6 which calls for the "product" being "characterized by the fact that the immobilization system contains components, which either suppress or prevent agglomeration of the blood", that heparin (or other materials) are used to antagonize agglomeration." There is no disclosure as to how this is done.

Page 23 of the Wagner translation appears to discuss the types of polymers used for encapsulation and mentions polyethylene oxide. Polymer films of various types are mentioned at the bottom off page 24 and the top of page 25 of the Wagner translation.

The only experiments described in Wagner appears to be based on the first form of membranes, namely capillary membranes (diagram I), and these experiments are described beginning at the bottom of page 26 of the translation in which it is mentioned that the functions of the islet cells are observed in "silicon" (silicone?) catheters.

To summarize, Wagner describes microcapsules used in transplantation surgery. The microcapsules are made of organic material (polylysin complexed alginate) and allow release of active substances, in particular insulin and insulin related substances. These capsules are filled with islets of Langerhans, and the objective is to have a controlled release of insulin through the microcapsules. The

disclosed microcapsules are approximately 0.5 mm in diameter, and have an inner volume which is many times larger than the volume of the encapsulated islets (see page 6, line 10 and page 7, lines 6-8, of the English translation).

It should be noted that Wagner discloses no other alternative than encapsulation (see for example page 5, line 7-10 and page 6, line 7-9, of the English translation). In particular, it should be noted that despite the fact that there is a discussion of the degree of free space inside the capsules and the effect thereof on e.g. the diffusion behavior, the only alternative suggested for enhancing the efficiency is to make the capsule smaller (see page 7, lines 9-13, of the English translation). Nowhere in Wagner is it even remotely suggested that the islets be coated in the sense of the present invention.

Soon-Shiong describes the encapsulation of islets by coating with polymerizable alginate or with a composite of alginate and polyethylene glycol. Heparin is mentioned in the Soon-Shiong specification only at column 6, line 60, among a basket or shot gun disclosure of biocompatible materials including polymerized saccharides such as alginates.

Soon-Shiong contains thirty-two examples, none of which mention heparin.

In the bottom paragraph of column 7 of Soon-Shiong, it is mentioned that a particularly preferred embodiment

utilizes a modified alginate capable of being polymerized and ionically cross-linked as the encapsulating polymer, wherein the alginate is modified to produce the compound A-X where A is a naturally occurring or synthetic modified form of alginate, and X is a moiety containing a pair of carbon atoms separated by a double or triple bond and capable of undergoing free radical polymizeration. Claim 5 specifies that when A is covalently linked to Y, A may be a polysaccharides selected from a group of materials including heparin.

Nomura describes a study undertaken "to evaluate the effects of various anticoagulants" including heparin "on portal vein pressure, recipient survival, and graft survival when unpurified islets are transplanted into the portal vein using the isograph model."

Under the heading "Materials and Methods" the following text appears:

> Unpurified islets were transplanted into the portal vein through a 24-gauge cannula over three minutes. Fifteen minutes after the start injection of the cells, portal vein pressure was measured. Recipients were divided into four groups.

Heparin or heparin plus other materials were "injected into the portal vein…."

The third declaration of Rolf Larsson, Ph.D., one of the co-inventors of the present invention, which Declaration was executed November 29, 2007, and filed with the reply of

December 10, 2007, states in paragraph (14) on page 5 as follows:

> (14) Newly relied upon Nomura…discloses only the use of heparin administered systemically. Systemic administration of heparin is likely to generate bleeding complications, and has nothing to do with our invention which relates to the use of surface-bound heparin which acts locally on the surface of the islets thus eliminating bleeding complications.

It is seen that Nomura does not disclose any treatment of the islets by incubation with heparin.

Couser relates to the systemic administration of a drug, and not to any transplantation of insulin producing cells. This publication appears to have nothing to do with either the present invention or any of the other cited references.

III. -Claims 4, 8, 11 and 27 define novel subject matter over Wagner.

Interpreting the difficult to understand Wagner as closely as possible to the present invention, a critical distinction is that the closest Wagner comes to the present invention is encapsulating islets within a polymer shell or capsule having a diameter of 0.5 mm, "a volume several times larger than that of the islets…, which are 50-300 μm in size." In the present invention, the islets are not encapsulated, but

are instead treated with a clotting preventing agent such as heparin.

Thus, contrary to claims 4, 8, 11 and 27, Wagner does not disclose "transplantation of insulin cells in the form of individually isolated islets…."

Contrary to claims 4, 8, 11 and 27, Wagner does not disclose that the "individually isolated islets are modified by irreversible absorption with a clotting inhibiting agent comprising heparin or a fraction or derivative thereof onto the surfaces of the islets,…."

Contrary to claims 4, 8 and 11, Wagner does not disclose "individual islets cells… each separately coated with heparin or a fraction or a derivative thereof by pre-incubation of islets in an aqueous solution containing heparin or a fraction or derivative thereof,…; or as recited in claim 27, the "modification comprising incubating said inlets a solution of heparin or a fraction [or] derivative thereof."

And, unlike the present invention "wherein said clotting inhibiting agent acts to inhibit or reduce clotting", there is no evidence whatsoever that anything disclosed by Wagner will produce such a result, i.e. there is no inherency because there is no reasonable certainty that any such result would be achieved in anything taught by Wagner.

As understood, the Examiner's position is that there is no difference between the encapsulation option of Wagner, in which heparin may optionally somehow be involved, and the

subject matter of Appellants' claims 4, 8, 11 and 27, but this is speculation on the part of the Examiner which not only goes far beyond any disclosure of Wagner, but which also is contrary to the evidence, including the declarations of record in this case.

Appellants submit and respectfully represent that it is clear to anyone skilled in the art upon reading Wagner that the capsule material is utilized as a measure to avoid immunological reactions, due to the fact that the capsule material exhibits poor compatibility with blood. The closest Wagner disclosure to the present invention is in the blending of the capsule material with heparin in claims 6 and 7. But there is no disclosure and/or teaching by Wagner to indicate that the islets per se might provoke clotting, which is an important discovery upon which the present invention is based. Wagner does not provide a disclosure which would enable one skilled in the art to practice appellants' claimed invention, *Impax Laboratories, Inc. v. Aventis Pharmaceuticals Inc.*, Fed.Cir., No. 2007-1512, 10/3/08.

The closest that Wagner comes to the present invention is in Wagner's claims 6 and 7 wherein, as best can be understood, Wagner teaches mixing of the anticoagulant, e.g. heparin, in the material used to form the capsules. The only way that one can read Wagner on Appellants' claims is by superimposing Appellants' disclosure on Wagner. Wagner simply does not disclose modifying the cells by irreversible

absorption of the clotting inhibiting agent as Appellants have claimed.

Contrary to the Examiner's position, there is a fundamental difference between encapsulation (the closest Wagner comes to the present invention) and modification by irreversible absorption of a clotting inhibiting agent in accordance with the present invention and as claimed. As supporting evidence, Appellants respectfully invite attention to the first declaration filed in this application on March 2, 2004, in the name of three of the inventors, namely Olle Korsgren, MD, PhD; Bo Nilsson, MD, PhD; and Rolf Larsson, PhD. This declaration states in part as follows:

> First, and in a general way, we can state as fact that our invention as set forth in the present application is not based on the same principles, i.e. encapsulation, as the Wagner et al citation DE 196 23 440 A 1 (hereinafter "Wagner") or the Soon-Shiong et al citation U.S. patent 5,705,270 (hereinafter "Soon-Shiong").

The declarence then provides more detail:

> The U.S. Examiner has stated (Advisory Action), "Coating and encapsulating appear to be the same." And that, "this appears to be a difference in nomenclature only." We state as fact that coating according to our invention is absolutely not the same as encapsulating according to Wagner and Soon-Shiong. Coating in accordance with our invention of the present U.S. Patent application does not result in encapsulation, but instead results in a linkage between the islets and the heparin or other clotting preventing agent, i.e. the "coating" according to our invention results in the isolated islets being modified by irreversible adsorption with the heparin, a

> physical condition which is entirely unlike encapsulation with a polymeric material as disclosed by Wagner and Soon-Shiong.

Microcapsules are, as disclosed and taught by Wagner, much larger than the islets, Wagner having stated at page 7 of the translation: "Most of the microcapsules of a diameter of half a millimeter have a volume several times larger than that of the islets…, which are 50-300 µm in size." The above noted first declaration states on page 3 as follows:

> Such microcapsules, including those produced according to the methods of Wagner and Soon-Shiong, consist of polymer spheres of 400-800 µm in diameter, typically made of alginate (a polysaccharide) or synthetic polymers, with a wall thickness of 10-50 µm to separate the encapsulated islets from their biological environment, the ultimate goal of the capsule shell being to establish an immunological barrier. Encapsulation implies a coherent material in the form of a sphere which is not integrated into the biological surface of the islets but rather holds a number of islets being dispersed in the interior of the spheres.

And, in the paragraph spanning pages 3 and 4 of the first declaration:

> The references of Wagner and Soon-Shiong therefore are very clearly concerned with encapsulation techniques, very different from our technique. As an example, both references teach the use of alginate as a vehicle to construct microcapsules. The encapsulation techniques according to Wagner and Soon-Shiong result, according to what is desired and clearly implied in these documents, in the islets being trapped and physically enclosed within the microspheres, i.e. within the capsule shells. As indicated above, this is a

> physical state which is quite different from what occurs according to our method.

Thus, no encapsulation occurs in accordance with the present invention.

As best understood, the Examiner believes and has taken the position that Corline Heparin Conjugate used in example 3 of the present application, having a polymer component, is therefore no different from Wagner, but this is not correct, because use of Corline Heparin Conjugate as in appellants' example 3 does not lead to encapsulation. Please see page 5 of the aforementioned first declaration, where the following statement of fact appears:

> In the case where the islets have been modified by e.g. the Corline Heparin surface (e.g. our Example 3), there are no prerequisites that would lead anyone skilled in the art to conclude that such a procedure involving simple mixing would represent encapsulation. The procedure implies (and results in) attachment to the biological structure of the islets of individual high-molecular weight molecules, with no semi-permeable function.
>
> ... In our invention, contrary to Wagner and Soon-Shiong, no such capsule is formed. The heparin in our invention does not encapsulate the islets. Even when a heparin-conjugate with alginate, e.g. the Corline heparin conjugate of Example 3 of our above-identified U.S. Patent application, is used, encapsulation of the islets does not occur.

And, the Declarants add at pages 6 and 7, the following:

> We state as fact that it is inherent in our above-identified U.S. patent application that the surface of each individual islet is modified to reduce thrombogenicity, and each

> islet is free to interact with the biological environment. No physical barrier and no immunological barrier heparin coating occurs in our invention. On a molecular level there is provided a thickness of heparin of at most 0.1 µm, which is non-coherently attached directly to the biological surface of the islets.
>
> Artificial encapsulation implies that a synthetic polymer is used to establish a physical barrier between the islets and the biological environment (tissue, blood, etc.) only to allow certain substances (e.g. insulin) to pass across the barrier. Our process of the present application may be referred to as non-artificial based on the fact that the islets are free to fully interact at a molecular scale with their biological environment and that they retain their capacity to release insulin without any passage through a semi-permeable membrane. The purpose of attaching e.g. heparin to the surface of the islets is entirely to down-regulate the tendency of the islets to induce coagulation and inflammation.
>
> We therefore state as fact that our islets, after "coating" with heparin, are not encapsulated.
>
> Our heparin-modified islets can be obtained by simple mixing of heparin or heparin complex with the islets, as in Example 3 of our U.S. patent application. On the other hand, in Wagner and Soon-Shiong there are required operations, which are the main focus of these documents, for the creation of the capsule shells, e.g. extrusion in a two-phase coaxial flow system according to Example 20 of Soon-Shiong, or an emulsification technique with a photo polymerization as set forth in Example 19 of Soon-Shiong.

What appears in a declaration is of course evidence, and the Examiner has no evidence to the contrary. Throughout prosecution of this application, the Examiner has essentially

disregarded the declarations in spite of the fact that the Declarants are experts in the art who are entitled to present expert opinion which must be considered, and further in spite of the fact that the Declarants submitted statements of fact based on their knowledge.

Appellants' position is supported by *In re Khelghatian*, 150 UPSQ 661,663, footnote 2 (CCPA 1966), wherein Judge Rich, speaking for the Court, and commenting on the Supreme Court's decisions in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459, and *United States v. Adams*, 383 U.S. 39, 148 USPQ 479, stated as follows: "In our view the Court there said nothing at all about 'doubtful cases,' nor in any way suggested that any record evidence should not be accorded its full probative weight…. Such an approach [brushing off a Declaration because the Examiner "is satisfied" that the invention is unpatentable] is reminiscent of the proverbial "don't bother me with the facts, my mind is made up" method of decision and has, we think, no place in the application of 35 U.S.C. 103. We therefore remain of the view that the law requires consideration of all ***evidence***, properly submitted, …." (emphasis in original; bracketed material added). Thus, all evidence is to be considered.

Also see *In re Alton*, 37 USPQ2d 1578, 1583 (Fed Cir 1996), relating to declarations of fact. Also see *Ex parte Copping*, 180 USPQ 475, 476, relating to opinion affidavits from experts.

Wagner discloses and seemingly denigrates a prior micro-capsulation system where the islets are enclosed in the smallest possible capsules (diameter of 0.5 mm) made of alginate complexed with polylysine, noting the English translation of the Wagner description on page 6, lines 7-10. The islets are much smaller (50-300μm), see pg. 7, line 8), so many fit within the micro-capsules. Wagner teaches providing an "artificial surface" forming a "mono-layer film" over "proteins" which have "selectively accumulate[d], noting page 13 at the bottom.

Wagner teaches the use of encapsulation, e.g. in the trial commencing at the bottom of page 27, 3000 islet cells were encapsulated on two microprotein silicon catheters. This implies that a definite number of cells (typically several hundred) are confined in a capsule, namely a compartment, defined by a semi-permeable membrane. An objective and apparent result of Wagner is platelet aggregation of blood (pg 17-19 of Wagner). This is distinctly different from the presently claimed invention which involves and teaches surface modification of each individual islet without changing the physical configuration of the islet.

The preferred route for transplantation of islets of Langerhans is to inject the isolated islets into the portal vein allowing the islets to settle in the liver. The result from an animal experiment where porcine islets were intraportally transplanted into pigs is found in appellants'

specification at page 5, lines 13-20. The method of intraportal transplantation can also be used in humans, and thus it is impossible to use the intraportal route if the cells have been enclosed in capsules of high molecular weight material that are considerably larger in size than the individual cells/islets.

Contrary to Wagner, in the present invention the heparin or modified heparin will be attached to each individual islet without changing the dimensions, i.e. the size which again is completely different from Wagner wherein the capsule is much, much larger than the size of individual cells.

As further evidence, the appellants submitted a second declaration, executed February 4, 2007, and again in the names of Dr's Korsgren, Nilsson and Larson, filed with the Reply of April 4, 2007, in which they stated as fact:

> Encapsulation (also referred to as microencapsulation) implies that the islets are confined within a polymer membrane that is not in direct contact with the islets. Extensive efforts have been spent on preparing microcapsules primarily using alginates as the capsules-forming material in accordance with what is disclosed in Wagner and Soon-Shiong.
>
> A recent article (ref. 1), Dufrane et al[1], is representative for the current state-of-the-art. As illustrated in Fig 1 in the

[1] 1. Dufrane D., Goebbels R-M., Saliez A., Guiot Y., and Gianello P.: Six-months survival of microencapsulated pig islets and alginate biocompatibility in primates. Proof-of-concept. Transplantation, 9, 1345-1353, 2006

> cited article, an optimal capsule should be a sphere with a diameter of 650- 700 µm. Wagner specifies a diameter of 500 µm (p. 6, item 2, l.3-4 in translated document).
>
> Considering that the islets have a size of 50-300 µm, we state fact beyond any doubt that one or several islets will be enclosed in each microcapsule with considerable dead space between the islet(s) and the enclosing membrane.

The Declarants then stated that even with the most advanced current technology "capsules of the prior art leave a dead space of 25-50 µm between the cell surface and the polymer membrane…." As a result, the "dead space creates delayed response times due to the fact that glucose must first defuse through the membrane, and then the glucose has to be transported by a concentration gradient across the dead space until it reaches the cell surface."

The Declarants continue near the bottom of page 3 of such declaration, as follows:

> On the contrary, in our invention, the material used, e.g. Corline Heparin Conjugate, is adsorbed directly in close contact with individual islets with no dead space, whereby glucose in blood interacts directly with the islet cells so that a physiological response with regard to release of insulin is achieved. The following picture (Fig. 2), prepared in our laboratory, shows one islet cell coated with heparin according to our invention and examined by confocal microscopy using fluorescently labelled antithrombin that binds to heparin. It is evident that the coating follows the contour of the cell and is in direct contact with the cell surface.

This declaration then presents a photomicrograph, Fig. 2, which shows that the islets treated according to the present invention have the heparin **on the surface of the islets.**

Appellants believe and respectfully submit that this is strong evidence which the Examiner has not and cannot rebut.

This second declaration then moves to another distinction at page 5, where the following statement appears in which the insoluble nature of the microcapsules of Wagner which form a membrane barrier, is contrasted with the present invention:

> There is another distinct difference between encapsulated islets such as those of Wagner and Soon-Shiong, and heparin coated islets according to our invention that needs to be emphasised. The spherical membrane that encapsulates the islets of the prior art is an insoluble polymer with a cross-longitudinal network of bonds (thus it forms a membrane barrier between the islet surface and the surroundings), whereas the material we use, e.g. Corline Heparin Conjugate, is a soluble macromolecule that is adsorbed as discrete molecules onto the cell surface with no cross-longitudinal linkages being formed between the conjugate molecules (thus no membrane barrier is formed between the islet surface and the surroundings).

The second declaration concludes as follows:

> As clearly explained in our previous Declaration, the encapsulating membrane composed of an insoluble polymer proposed by Wagner et al and Soon-Shiong et al constitutes a barrier to immunologically active cells and molecules, whereas no such barrier is created by adsorption of the heparin, e.g. Corline Heparin Conjugate. We reiterate with strong emphasis that it is

> absolutely clear and certain that the chemical constitution and diffusion characteristics are fundamentally different between the two methods, and that there is no chemical or technical rationale on basis of which one could accurately maintain that adsorption of the Corline Heparin Conjugate would lead to encapsulation in the sense of Wagner et al and Soon-Shiong et al.

Appellants again respectfully note there is no evidence to the contrary.

Further evidence in support of appellants' position exists in the form of the third declaration of Professor Larsson executed November 29, 2007, and the declaration of independent expert James Shapiro MD, PhD, executed December 8, 2007, both of such declarations having been filed with the Reply of December 10, 2007.

In his declaration, Professor Shapiro states as follows:

> I understand from reading the specification of the above-identified application 09/890,936 that the individually isolated islets are treated with a clotting inhibiting agent, e.g. heparin or soluble Corline heparin conjugate, which is adsorbed onto the surface of the individual isolated islets. This adsorption of clotting inhibiting agent onto the individual isolated islets is quite different from islet encapsulation, the latter of which refers specifically to immunological isolation of islets from attacking immune damaging cells.

The adsorption of clotting inhibiting agent "is quite different from islet encapsulation."

At most, what Wagner discloses is an encapsulation of islets with an insoluble polymer shell, e.g., polyamide, polyester, polyolefin, etc., namely an insoluble barrier, something quite contrary to the present invention where the heparin material is adsorbed onto the cell surface with no formation of a barrier shell. Indeed, one end of the molecule is adsorbed onto the cell surface, and the other end protrudes out from the cell. Such molecules, e.g. heparin and Corline Heparin Conjugate, are water soluble molecules. The so treated islets do not delay insulin response by the cell, because there is no membrane barrier that has to be penetrated by glucose and insulin, as inevitably must occur in the prior art, including Wagner. Further in this regard, and in support of Appellants' position, attention is invited to page 3 of the Declaration of Dr. James Shapiro, executed December 8, 2007, and filed with the reply of December 10, 2007.

The present invention differs fundamentally from Wagner in not providing an impenetrable shell around the islets.

The Examiner relies on claim 8 of Wagner, but claim 8 does not disclose the use of heparin or anything similar to heparin. Please see paragraph 8 of the third Declaration of Professor Larsson. Claim 7 of Wagner does mention heparin "used to antagonize agglomeration", but Wagner does not describe how heparin might be used in the Wagner system;

please see paragraph (9) of Professor Larsson's third Declaration.

As Dr. Larsson pointed out during the interview of June 28, 2007, the Examiner's interpretation of Wagner makes no sense, because, if cells of Wagner were first mixed with an anticoagulant and then encapsulated as proposed by the Examiner at page 4 of the Official Action of August 9, 2007, the anticoagulant could not function because the anticoagulant would then be sealed within the microcapsule. This is confirmed as fact in paragraph 11 of the Third Declaration of Professor Larsson.

As to the fundamental difference between encapsulation (the prior art) and coating, please also see the first Declaration of Drs. Korsgren, Nilsson and Larsson executed in February of 2004 and filed with a "Second Preliminary Amendment for Continued Examination" of March 2, 2004; and the second Declaration of Drs. Korsgren, Nilsson and Larsson, filed with the Reply of April 4, 2007.

There is no basis for the rejection based on Wagner, and such rejection should be reversed. Such is respectfully requested.

IV. Claim 4, 8, 11 and 27 define novel subject matter over Soon-Shiong

Soon-Shiong discloses little more than Wagner, except Soon-Shiong is much more clear. But, like Wagner, Soon-Shiong relates to **encapsulation** of the islets, something fundamentally different from the present invention as already explained above, and as established by the evidence of the declarations of record also referred to above.

Thus, Soon-Shiong discloses the microencapsulation of biological materials using, for example, a polymerizable alginate or a composite thereof with polyethylene glycol. The present invention does not involve, and appellants do not claim, any such subject matter, because the present invention does not involve or comprise encapsulation of islets of Langerhans.

It is well known that the main reason for using encapsulation is to avoid immunological reactions aiming at eliminating the need for immunosuppressive therapy. In Soon-Shiong, an encapsulation system is disclosed (see col. 3, lines 53-61, and abstract) which comprises compounds which are capable of undergoing free radical polymerization e.g. by using certain sources of light. The objective of Soon-Shiong is to provide an encapsulation which allows delivery of substances from the insides of the capsule, i.e. drug delivery or insulin secretion from encapsulated islets of Langerhans, while providing immunoprotection. The Soon-Shiong patent does

not disclose features of clotting prevention, and thus teaches away from the presently claimed invention.

Appellants respectfully add, as already noted above, that the Examiner was unjustified in ignoring the evidence of the Declarations of record where the Declarants stated as fact as follows at page 7:

> We therefore state as fact that our islets, after "coating" with heparin, are not encapsulated.
>
> Our heparin-modified islets can be obtained by simple mixing of heparin or heparin complex with the islets, as in Example 3 of our U.S. patent application. On the other hand, in Wagner and Soon-Shiong there are required operations, which are the main focus of these documents, for the creation of the capsule shells, e.g. extrusion in a two-phase coaxial flow system according to Example 20 of Soon-Shiong, or an emulsification technique with a photo polymerization as set forth in Example 19 of Soon-Shiong.

The Examiner was not justified in speculating contrary to the statements of fact in the Declarations of record.

To the extent that the Examiner seems to be relying on inherency, appellants respectfully note that reliance by the PTO on inherency in a reference requires that such inherency must be reasonably certain. For example, please see *In re Brink*, 164 USPQ 247, 249:

> Absent a showing [by the PTO] of some **reasonable certainty** of inherency, the rejection... under 35 U.S.C. 102 must fail. (emphasis added)

Also see *Ex parte Cyba,* 155 USPQ 756, 757 (1967), and *In re Oelrich,* 212 USPQ 323, 326 (1981). There is no reasonable certainty that anything done by Soon-Shiong and disclosed in Soon-Shiong would provide anything identical or even similar to the present invention. Therefore, inherency in Soon-Shiong (or Wagner) is neither inevitable nor reasonably certain, and no inherency exists which can be relied upon.

Further in this regard, although claim 5 of Soon-Shiong mentions heparin as a possible alternative compound for apparently forming a co-monomer for formation of the polymer shell used in forming the microcapsules, there is no disclosure and no teaching how heparin could be applied to individual islets. Reading Soon-Shiong, like reading Wagner, does not enable one skilled in the art to reach appellants' subject matter.

At one point, the Examiner argued that "it is unclear how the heparin-alginate conjugate of the Corline system differs from the heparin/alginate system of Soon-Shiong." It is perfectly clear that there are distinct differences. Corline's heparin-amine conjugate (not alginate) can be added directly to the culture medium without affecting the dimensions of the islets. In the description of the present invention, page 10, lines 14-20, it is concluded that the surface modification of the islets by heparin is expected to decrease or even eliminate the need for insulin injections. This clearly implies that the surface modification does not

change the insulin excretion of the islets. But according to Example 25 in Soon-Shiong, a rather elaborate procedure has to be applied involving co-extrusion and photo-crosslinking. There is no provision that the islets will remain as individual islets maintaining their original dimensions.

Soon-Shiong, like Wagner, does not disclose a method as called for in claims 4 and 27 "wherein said individual isolated islets are modified by an irreversible adsorption with a clotting inhibiting agent comprising heparin or a fraction or derivative thereof". There is nothing in either Wagner or Soon-Shiong which has anything to do with irreversible adsorption. This feature is neither disclosed in the references nor is it inherent in the references, as is further made clear in the second declaration of the inventors. Again, please also see page 3 of Dr. Shapiro's Declaration, and also paragraphs (12) and (13) on pages 4 and 5 of Professor Larsson's third Declaration, as well as the first and second Declarations of the inventors.

Appellants again respectfully note that it is fundamental that the Declarations are evidence, not arguments. What is stated as fact must be accepted, and what is set forth as expert opinion must also be accepted, in the absence of evidence to the contrary, of which there is none.

The present invention relates to and describes how to modify the surface of individual islets so they can be brought into direct contact with blood without encapsulating

the islets, without having to introduce artificial materials such as used by both Wagner and Soon-Shiong, and without causing the blood to clot. In contrast, both Wagner and Soon-Shiong mention heparin as an example of a substance to be used to reduce the deleterious effect of the artificial material used to encapsulate the islets. Both Wagner and Soon-Shiong aim to shield the islets from direct contact with the blood. There is a clear and distinct difference between the present invention and both Wagner and Soon-Shiong.

Soon-Shiong does not anticipate Appellants' claim, and the rejection should be reversed. Such is respectfully requested.

V. -Claims 4, 8 and 11 are not anticipated by Nomura

The third declaration of Rolf Larsson, Ph.D., one of the co-inventors of the present invention, which Declaration was executed November 29, 2007, and filed with the Reply of December 10, 2007, states in paragraph (14) on page 5 as follows:

> (14) Newly relied upon Nomura…discloses only the use of heparin administered systemically. Systemic administration of heparin is likely to generate bleeding complications, and has nothing to do with our invention which relates to the use of surface-bound heparin which acts locally on the surface of the islets thus eliminating bleeding complications.

Applicants' claims do not recite administering heparin. Instead, the heparin used in the present invention has been applied to the individual islets, and it is these surface-treated islets which are administered to the patient.

The rejection should be reversed, and such is respectfully requested.

VI. -Claim 9 defines novel and non-obvious subject over Soon-Shiong and Wagner in view of Couser.

The deficiencies of Wagner and Soon-Shiong have been pointed out above and Couser has not been cited to make up for those deficiencies (and indeed does not do so). Actually, Couser has nothing to do with either the present invention or the primary references. Thus, Couser is fundamentally irrelevant to the present invention as stated **as fact** in paragraph 15 of the third declaration of Professor Larsson. Couser clearly relates to the systemic administration of a drug, and not to any transplantation of insulin producing cells which have already been modified as recited in claim 4, together with the added subject matter of the dependent portion of claim 9.

Claim 9 defines non-obvious subject matter and the rejection should be reversed. Such is respectfully requested.

CONCLUSION

Appellants respectfully submit that the Examiner has not met the burden of establishing lack of novelty for claims 4, 8, 11 and 27, or the additional burden of the establishing a *prima facie* case of obviousness for claim 9. Appellants respectfully request reversal of the rejections.

Respectfully submitted,

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CLAIMS APPENDIX

4. A method comprising

transplantation of insulin producing cells in the form of individually isolated islets to a patient suffering from insulin dependent diabetes mellitus (IDDM),

wherein said individually isolated islets are modified by irreversible adsorption with a clotting inhibiting agent comprising heparin or a fraction or derivative thereof onto the surfaces of the islets,

wherein said individual islet cells are each separately coated with heparin or a fraction or derivative thereof by preincubation of islets in an aqueous solution containing heparin or a fraction or derivative thereof,

wherein said clotting inhibiting agent acts to inhibit clotting or reduce clotting.

8. The method according to claim 4, wherein more than one clotting inhibiting agent is used.

9. The method according to claim 4, wherein the clotting inhibiting agent is supplemented by an inhibitor of complement.

11. A method for increasing survival of islet cells according to claim 14, in connection with transplantation of insulin producing cells to patients with insulin dependent diabetes mellitus (IDDM), comprising inhibiting of clotting, monitored as reduced generation of thrombin-antithrombin complex (TAT complex).

27. A method comprising transplantation of insulin producing cells in the form of isolated islets to a patient suffering from insulin dependent diabetes mellitus (IDDM),

wherein said isolated islets are modified by irreversible adsorption of a clotting inhibiting agent comprising heparin or a fraction or derivative thereon [*sic*-should be "thereof"] onto the surface of the islets;

said modification comprising incubating said islets in a solution of heparin or a fraction of [*sic*-should be "thereof"]derivative thereof;

wherein said clotting inhibiting agent acts to inhibit or reduce clotting.

EVIDENCE APPENDIX

Copies of the Declarations of record, referred to above, are attached hereto. All of such declarations were entered as a matter of right.

DECLARATION UNDER 37 CFR 1.132
filed and entered March 2, 2004

SECOND DECLARATION UNDER 37 CFR 1.132
filed April 4, 2007; and entered June 5, 2007

THIRD DECLARATION OF ROLF LARSSON
filed and entered December 10, 2007

DECLARATION OF JAMES SHAPIRO, M.D., PH.D., FRCSC
filed and entered December 10,2007

RELATED PROCEEDINGS APPENDIX

There are no related proceedings in connection with the subject application.